## AMENDMENT

Kindly amend the application, without prejudice, without admission, without surrender of subject matter and without any intention of creating any estoppel as to equivalents, as follows.

**IN THE SPECIFICATION:**

Kindly amend the specification, without prejudice, without admission, without surrender of subject matter and without any intention of creating any estoppel as to equivalents, to read as follows:

Page 23, line 13, kindly rewrite the paragraph thereat to read as follows:

Known inhibitors of retinal dehydrogenase include Citral and ~~Disulphram~~ Disulphiram (aka disulfiram).

Page 33, line 23 to page 34, line 3, kindly rewrite the paragraph thereat to read as follows:

The manifestations of hyperthyroidism (and diseases associated with hypothyroidism) include ~~aggitation~~ agitation, anxiety, loss of weight, diarrhoea, tachycardia and menstural disorders The manifestations of hypothyroidism (and diseases associated with hypothyroidism) include dementia, Depression, Cold intolerance, obesity, alopecia, dry skin/eczema, lethargy, bradycardia/heart block, haematological eg anaemia, reduced metabolism, changes in lipid metabolism, constipation, glucose intolerance and menstural disturbances. Each of these is suitable for treating or alleviating with the methods and compositions described here.

Page 73, line 19, to page 74, line 5, kindly rewrite the paragraph thereat to read as follows:

A skin penetration enhancer which is dermatologically acceptable and compatible with the blocking agent or retinol binding protein receptor antagonist or inhibitor of a retinoic acid synthesis enzyme (including retinol dehydrogenase and retinal dehydrogenase) can be incorporated into the formulation to increase the penetration of the active compound(s) from the skin surface into ~~epidemal~~ epidermal keratinocytes. A skin enhancer which increases the absorption of the active compound(s) into the skin reduces the amount of blocking agent or

retinol binding protein receptor antagonist, etc needed for an effective treatment and provides for a longer lasting effect of the formulation. Skin penetration enhancers are well known in the art. For example, dimethyl sulfoxide (U.S. Pat. No. 3,711,602); oleic acid, 1,2-butanediol surfactant (Cooper, J. *Pharm. Sci.*, 73:1153-1156 (1984)); a combination of ethanol and oleic acid or oleyl alcohol (EP 267,617), 2-ethyl-1,3-hexanediol (WO 87/03490); decyl methyl sulphoxide and Azone (Hadgraft, *Eur. J. Drug. Metab. Pharmacokinet*, 21:165-173 (1996)); alcohols, sulphoxides, fatty acids, esters, Azone, pyrrolidones, urea and polyoles (Kalbitz et al, *Pharmazie*, 51:619-637 (1996)).

Page 27, lines 8 to 18, kindly rewrite the paragraph thereat to read as follows:

Nuclear receptors include receptors for glucocorticoids (GRs), androgens (ARs), mineralocorticoids (MRs), progestins (PRs), estrogens (ERs), thyroid hormones (TRs), vitamin D (VDRs), retinoids (RARs and RXRs), peroxisomes (XPARs and PPARs) and icosanoids (IRs). A nuclear receptor response element may therefore include a retinoic acid receptor response element (RARE), a vitamin D response element (VDRE), a thyroid hormone receptor response element or a peroxisome proliferator-activated receptor (PPAR) response element. Other response elements include chicken ovalbumin upstream transcription factor (COUP-FF) response element and the apoAI regulatory protein-1 (ARP-1) response element. ~~Thus, the methods as described here~~ Such a method comprises reducing the endogenous level or activity of retinoic acid (RA) in a cell of the patient, as described elsewhere in this document.

Page 29, lines 5 to 11, kindly rewrite the paragraph thereat to read as follows:

Nuclear receptors can exist in a variety of isoforms. For example, GR subfamily members have usually one receptor encoded by a single gene, although there are exceptions. For example, there are two PR isoforms, A and B, translated from the same mRNA by alternate initiation from different AUG codons. There are two GR forms, one of which does not bind ligand. The thyroid receptor usually has several receptors that are encoded by ~~at~~ two (alpha and beta) genes, while RAR, RXR, and PPAR receptors are encoded by three (alpha, beta and gamma) genes. Alternate RNA splicing may also give rise to isoforms.

Page 31, lines 1 to 8, kindly rewrite the paragraph thereat to read as follows:

A list of genes whose promoters comprise retinoic acid response elements is shown in ~~Appendix A~~ Appendix 1. Expression of such genes is modulated by RAREs. Diseases characterised by, or associated with, over-, ectopic or otherwise abnormal expression of such genes include psoriasis, acne, photoageing, cancer, acute promyelocytic leukaemia, psoriasis, disorders of keratinisation e.g. the ichthyoses and keratodermos, acne vulgaris and acne rosacea, lichen planus, cutaneous lupus erythematosus, pre-malignant conditions, e.g. melanocytic naevus, mrelodysplastic syndrome, among others. Such diseases, and others are suitably treated by the methods described here.

Page 31, lines 13 to 16, kindly rewrite the paragraph thereat to read as follows:

A list of genes whose promoters comprise vitamin D response elements is shown in ~~Appendix A~~ Appendix 1. Expression of such genes is modulated by VDREs. Diseases characterised by, or associated with, over-, ectopic or otherwise abnormal expression of such genes include psoriasis and other diseases and are suitably treated by the methods described here.

Page 32, lines 14 to 18, kindly rewrite the paragraph thereat to read as follows:

Tissue and species responses to PPs depend on pharmacokinetics, relative abundance of PPAR isotypes, nature of PPRE in the upstream regions of target genes, the extent of competition or cross-talk among nuclear transcription factors for PPAR heterodimerization partner retinoid X receptor and the modulating role of coactivators and corepressors on ligand-dependent transcription of PPARs.

Page 33, line 22 to page 34, line 3, kindly rewrite the paragraph thereat as follows:

The manifestations of hyperthyroidism (and diseases associated with hypothyroidism) include aggitation, anxiety, loss of weight, diarrhoea, tachycardia and menstural disorders. The manifestations of hypothyroidism (and diseases associated with hypothyroidism) include dementia, ~~Depression~~ depression, ~~Cold~~ cold intolerance, obesity, alopecia, dry skin/eczema, lethargy, bradycardia/heart block, haematological eg anaemia, reduced metabolism, changes in lipid metabolism, constipation, glucose intolerance and menstural disturbances. Each of these is suitable for treating or alleviating with the methods and compositions described here.

Page 56, line 19 to page 57, line 4, kindly rewrite the paragraph thereat to read as follows:

Thus, any of the above conditions may be treated or alleviated by the methods and compositions described here. In particular, the methods and compositions described are useful for treating any tumour, carcinoma, etc, which has been treated successfully or unsuccessfully with retinoid therapy. The methods and compositions are also useful to treat pre-malignant conditions i.e. to prevent their progression to actual malignancy. Reduction in endogenenous retinoic acid levels inhibits angiogenesis, and therefore such reduction may be used to prevent the spread of tumours. In particular, such reduction in endogenous retinoic acid levels may be achieved by antagonising the retinol binding protein receptor, preferably in such a way as to prevent retinol binding protein and/or retinol uptake. Reduction in endogenous retinoic acid levels may also be achieved by inhibiting or preventing synthesis of retinoic acid, by for example, inhibiting a retinoic acid synthesis enzyme as described elsewhere in this document. Specific examples of tumours include ~~include~~ melanocytic naevus and mrelodysplastic syndrome.

Page 57, lines 10 to 16, kindly rewrite the paragraph thereat to read as follows:

The common medical meaning of the term "neoplasia" refers to "new cell growth" that results as a loss of responsiveness to normal growth controls, e.g. to neoplastic cell growth. A "hyperplasia" refers to cells undergoing an abnormally high rate of growth. However, as used herein, the terms neoplasia and hyperplasia can be used interchangably, as their context will reveal, referring ~~to~~ generally to cells experiencing abnormal cell growth rates. Neoplasias and hyperplasias include "tumors," which may be either benign, premalignant or malignant.

Page 76, line 17, to page 80, line 9, kindly rewrite the paragraph therat to read as follows:

Paragraph 1. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises administering to the patient an antagonist of a retinol binding protein receptor (RBPr).

Paragraph 2. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises blocking the activity of a retinol binding protein receptor (RBPr) in cells of the patient.

Paragraph 3. A method of treating a patient suffering from a hyperproliferative disorder or photoageing, which method comprises lowering the endogenous level of retinoic acid (RA) in cells of the patient.

Paragraph 4. A method according to Paragraph 2 or 3, in which the method comprises administering to the patient an antagonist of a retinol binding protein receptor (RBPr).

Paragraph 5. A method according to Paragraph 2, 3 or 4, in which the endogenous level of retinoic acid is lowered in a hyperproliferating cell or a cell suffering from photoageing of said patient.

Paragraph 6. A method according to any of Paragraphs 2 to 5, in which the endogenous level of retinoic acid in the cell is lowered to the extent that cell proliferation is reduced or abolished.

Paragraph 7. A retinol binding protein receptor antagonist for use in a method of treatment of a patient suffering from a hyperproliferative disorder or photoageing.

Paragraph 8. An agent capable of lowering the endogenous level of retinoic acid in a cell for use in a method of treating a hyperproliferative disorder or photoageing in a patient.

Paragraph 9. An agent according to Paragraph 8, which is an antagonist of a retinol binding protein receptor (RBPr).

Paragraph 10. A method according to Paragraph 1 or 4, or an agent or antagonist according to Paragraph 7, 8 or 9, which is an immunoglobulin.

Paragraph 11. A method according to Paragraph 1 or 4, or an agent or antagonist according to any of Paragraphs 7 to 10, in which the agent is an antibody capable of binding to retinol binding protein receptor.

Paragraph 12. A method according to Paragraph 1 or 4, or an agent or antagonist according to Paragraph 7, 8 or 9, in which the agent is a peptide comprising a sequence from a receptor binding region of retinol binding protein.

Paragraph 13. A method, agent or antagonist according to Paragraph 12, in which the peptide has a sequence selected from: K29 - Q38, G59 - A71 and M88 - D102 of retinol binding protein and a heterodimer consisting of peptides G59 - A71 and M88 - D102.

Paragraph 14. A method according to Paragraph 1 or 4, or an agent or antagonist according to Paragraph 7, 8 or 9, which is an antisense compound capable of inhibiting the expression of retinol binding protein receptor.

Paragraph 15. A method, agent or antagonist according to Paragraph 14, which is an antisense RNA or an antisense DNA.

Paragraph 16. A method, agent or antagonist according to Paragraph 14 or 15, which an antisense molecule is a oligonucleotide.

Paragraph 17. A method, agent or antagonist according to any preceding Paragraph, in which the hyperproliferative disorder is psoriasis, acne vulgaris, or cancer.

Paragraph 18. A method for identifying an antagonist of retinol binding protein receptor, the method comprising contacting a cell with expresses retinol binding protein receptor with a candidate compound and determining whether the level of retinoic acid in said cell is lowered as a result of said contacting.

Paragraph 19. A method for identifying a compound capable of lowering the endogenous level of retinoic acid in a cell which method comprises contacting a cell which expresses a retinol binding protein receptor with a candidate compound and determining whether the level of retinoic acid in said cell is lowered as a result of said contacting.

Paragraph 20. A method for identifying a compound capable of inhibiting the interaction between a retinol binding protein and a retinol binding protein receptor, which method comprises contacting a retinol binding protein receptor, or a fragment thereof capable of binding retinol binding protein, with a candidate compound in the presence of retinol binding protein and determining whether the levels of retinol binding protein binding to the receptor are reduced.

Paragraph 21. A method of reducing proliferation of a hyperproliferative cell which method comprises blocking the activity of a retinol binding protein receptor of the cell.

Paragraph 22. A method according to any preceding Paragraph, which method further comprises the step of contacting the cell with an antagonist of a retinol binding protein receptor.

Paragraph 23. A method according to any preceding Paragraph, in which the endogenous levels of retinoic acid in said cell are lowered.

Paragraph 24. A method of causing a hyperproliferative cell to differentiate which method comprises blocking the activity of a retinol binding protein receptor of the cell.

Paragraph 25. A method of treating or alleviating the symptoms of a patient suffering from a retinoid sensitive disorder, which retinoid sensitive disorder is a disorder which is treatable by administration of retinoids, which method comprises blocking the activity of a retinol binding protein receptor in cells of the patient.

Paragraph 26. A method according to Paragraph 25, in which the retinoid sensitive disorder is a disorder which is treated or whose symptoms are alleviated by administration of higher than physiological levels of retinoid to the patient.

Paragraph 27. A pharmaceutical composition suitable for treating a patient suffering from a hyperproliferative disorder or photoageing, comprising a therapeutically effective amount of a retinol binding protein receptor antagonist together with a pharmaceutically acceptable carrier or diluent.

Paragraph 28. A compound or antagonist identified by a method according to Paragraph 18, 19 or 20.

Page 120, lines 18 to 19, kindly rewrite the paragraph thereat to read as follows:

2. A method according to ~~Claim 1~~ paragraph 1, in which the endogenous level of retinoic acid is lowered in a hyperproliferating cell or a cell suffering from photoageing of said patient.